remissions than seen in the AIM study, and longer follow-up will show if this translates into prolonged remission durations and at what toxicity cost. Recognizing the trial was not designed to compare treatment arms, it is striking that the outcomes in ARM A were similarly favorable to ARM B, with less associated toxicity and challenges the role of triplet therapy over the ideal doublet. There is a paucity of data with obinutuzumab in MCL, but this compares favorably to the remissions seen in combination with rituximab[9] and supports further trials utilizing obinutuzumab as the preferred anti-CD20 antibody. Nonchemotherapeutic frontline regimens are likely the future in MCL with the potential to be highly active and reasonably well tolerated. The rate of clinical and molecular remissions in these 14 treatment-naive patients, along with the improved toxicity profile compared with the relapsed cohort, warrant this triplet to be prioritized for further study, particularly in those with high-risk disease features. Whether ibrutinib will be the preferred BTKi in combination remains to be seen. Fixed duration therapy in combinations that induce high rates of molecular remission provide the ability to spare ongoing toxicity, including the financial toxicity seen with these agents. The role of retreatment at relapse in such scenarios remains unclear.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Curtis et al, page 896

New is forgotten old: IMiDs against chronic GVHD

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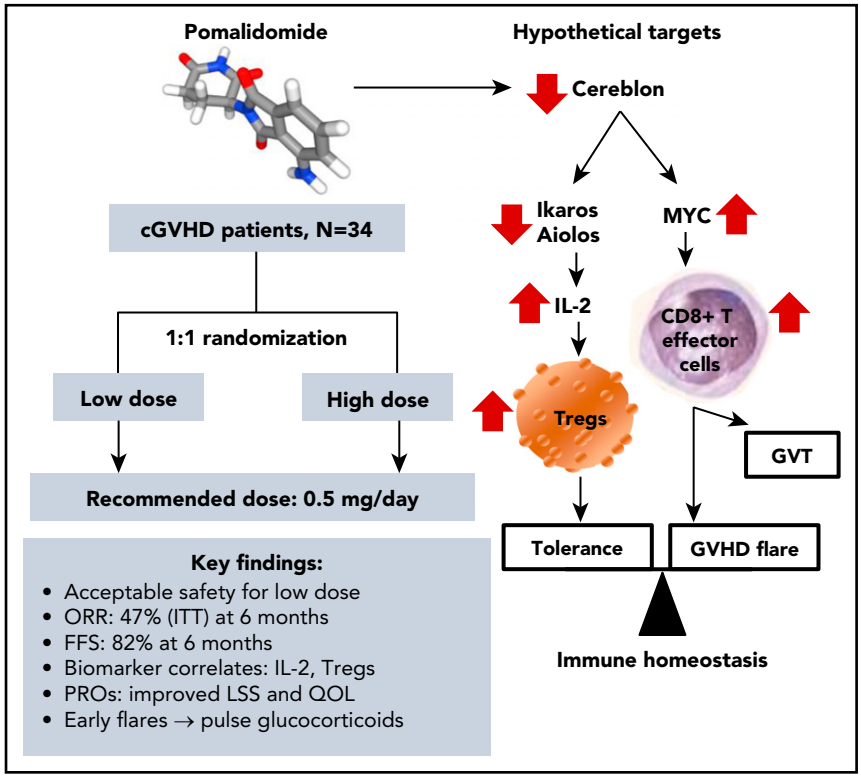
In this issue of *Blood*, Curtis et al present the results of a randomized phase 2 trial demonstrating activity and safety of pomalidomide for advanced chronic graft-versus-host disease (cGVHD) with fibrotic manifestations involving joint, fascia, and skin. This article is of a broad interest to hematologists and hematopoietic cell transplantation (HCT) providers, since it addresses an unmet medical need for patients with glucocorticoid-refractory cGVHD with advanced fibrotic manifestations.[1]

The high potency of pomalidomide is paired with more favorable toxicity profile compared with its structurally related immunomodulatory drugs (IMiDs). While thalidomide demonstrated variable efficacy in multiple trials of cGVHD,[2] it currently has a very limited use in advanced cGVHD, as its potentially effective dose of ≥200 mg/day is often associated with excessive neurologic, gastrointestinal, and hematologic toxicities. A broader use of lenalidomide in GVHD was halted by the risks of myelosuppression and GVHD propagation. Notably, lenalidomide maintenance after allogeneic HCT in patients with multiple myeloma increased incidence of acute GVHD in pivotal HOVON 76 and 07-REV trials.[3,4] The multicenter study by Curtis et al extends findings from the prior early-phase trial of pomalidomide in a smaller group of allograft recipients with glucocorticoid-refractory moderate-to-severe cGVHD.[5] Despite promising early efficacy, pomalidomide was poorly tolerated at the dose of 3 mg/day in that trial.[5] The phase 2 trial by Curtis et al has determined oral pomalidomide 0.5 mg/day as the optimal therapeutic dose for future use in sclerotic cGVHD (see figure).

Patients with extensive sclerotic cGVHD are often refractory to available therapies and have poor overall survival.[6] Curtis et al demonstrate that pomalidomide benefits fibrotic phenotypes of cGVHD. Imatinib and rituximab were compared in a randomized phase 2 trial of cGVHD patients with cutaneous sclerosis, but both led to suboptimal significant clinical responses at 6 months (26% and 27%, respectively).[7] In this study by Curtis et al, the overall response rate to pomalidomide was 47% in an intent-to-treat analysis and 67% among all evaluable patients at 6 months. Significant improvements in joint/fascia National Institutes of Health scores and skin involvement were achieved in patients with a median of 5 prior lines of therapy and 5 organs affected by cGVHD. Such heavily pretreated patients include a representative real-world sample of the cGVHD population impacted by substantial disability, morbidity, and impaired quality of life.

Failure-free survival has emerged as an important composite study end point of treatment change, nonrelapse mortality, and recurrent malignancy, used across



Pomalidomide therapy for cGVHD: trial highlights and immunomodulatory targets. FFS, failure-free survival; GVT, graft-versus-tumor; IL-2, interleukin-2; ITT, intent-to-treat; LLS, Lee symptom scale; ORR, overall response rate; PROs, patient-reported outcomes; QOL, quality of life; Tregs, regulatory T-cells.

clinical trials of cGVHD. Curtis et al report a noteworthy FFS of 82% at 6 months which compares favorably to the benchmark of 56% at 6 months after second line therapy of cGVHD.[8] According to Curtis et al, treatment failures (1-FFS) were largely attributed to the change of therapy (48%) yet very limited nonrelapse mortality (3%). The positive results of this trial are further strengthened by clinically meaningful improvements in Lee symptom scale and other patient-reported outcomes.[1]

Pomalidomide has a potent stimulatory effect leading to overproduction of IL-2 among multiple other cytokines.[2] Increased IL-2 levels observed in this trial are consistent with an established effect of pomalidomide, and the concomitant increase in the Treg fraction is likely secondary to the IL-2 burst. The complex immunomodulatory effects of pomalidomide may vary across the key phases of cGVHD pathobiology involving tissue damage, adaptive immunity, and end-organ fibrosis. Recent advances in cGVHD biology have underscored the critical role of Treg cells in restoring immune tolerance and balancing inflammatory responses related to T helper type 17/type 17 $CD8^+$ T cell upregulation as the cornerstones of cGVHD pathogenesis.[9] Thus, one of the mechanisms of pomalidomide suppression of cGVHD appears to be IL-2 upregulation and expansion of Treg cells (see figure). Obviously, pomalidomide does not consistently induce stable tolerance, because a fraction of patients experienced cGVHD recurrence when the drug was stopped.[1]

Curtis et al observed no relapsed malignancy with the use of pomalidomide within 2 years of follow-up. While cGVHD has been previously associated with less relapse after HCT, this observation suggests a potential role of pomalidomide in sparing or even augmenting the graft-versus-tumor effect. By targeting cereblon, IMiDs can generate metabolically hyperactive human $CD8^+$ T cells with effector phenotype and thereby enhance antitumor activity.[10] In mice, the antitumor effect of cereblon modulating compounds was also accompanied by accelerated GVHD.[10] Perhaps such a "double-edged sword" effect of pomalidomide might explain early flares (within 6 months) of cGVHD among ~18% of the trial participants as reported by Curtis et al.

Altogether, this novel, well-designed, well-conducted trial provides compelling evidence for adding pomalidomide to current treatment armamentarium of glucocorticoid-refractory sclerotic cGVHD. These data also support using pomalidomide for future trials incorporating experimental and/or the standard of care comparator arms. As novel therapies for cGVHD continue to emerge, it becomes increasingly important to tailor each one of those to an individual patient based on clinical cGVHD phenotypes, pathophysiologic mechanisms (eg, inflammatory and fibrotic), and underlying immune dysregulation. Besides facilitating personalized therapy for cGVHD, such insights will also inform rationale drug combinations as well as an understanding of which patients are expected to derive most clinical benefit from IMiDs, Janus kinase, Bruton tyrosine kinase inhibitors, or numerous other promising therapies being developed for cGVHD.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Meurer et al, page 923

The immunopeptidome guides permissive HLA mismatch

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In this issue of *Blood*, Meurer et al[1] report on the mechanistic underpinning of permissive HLA-DPB1 mismatch using mass spectrometry–based analysis of the HLA-DP immunopeptidome, T-cell receptor β (TCRβ) clonotype sequencing, and exploration of HLA-DM–mediated peptide editing. Permissive HLA-DPB1 mismatches show greater overlap in their HLA-presented peptide repertoire compared with their nonpermissive counterparts. This results in both a lower frequency and diversity of alloreactive TCRβ clonotypes (see figure), which could be reversed by silencing of the peptide editor HLA-DM.

The graft-versus-leukemia (GVL) effect following allogeneic stem cell transplantation still represents one of the most compelling examples of cancer immunotherapy. Since the first transplantation for leukemia, reported by E. Donnall Thomas in 1957, the optimal equilibrium of T-cell alloreactivity sufficient for the GVL effect, but not for severe graft-versus-host disease (GVHD), has been the fundamental goal of allogeneic hematopoietic stem cell therapy (HCT). The discovery and delineation of HLAs enabled matching between donors and recipients but also allowed for the identification of the peptide antigens presented via these molecules on the cell surface called the immunopeptidome. In recent years, in-depth immunopeptidome analyses of various cancer entities, including hematological malignancies, enabled the identification and characterization of the targets of anticancer T-cell responses and paved the way for the understanding, optimization, and new development of T-cell–based immunotherapies, including HCT.[2] In contrast to HLA-matched sibling donors, where minor histocompatibility antigens almost exclusively represent the targets of T-cell alloreactivity, most HLA-matched unrelated donors (UDs) additionally present mismatches for the HLA-DP antigens eliciting direct alloreactive T-cell responses with important implications for both GVHD and GVL. Increasing evidence suggested that donor-recipient disparities for HLA-DPB1 can be of clinical importance.[3] HLA-DPB1 mismatch was reported to elicit a wide range of alloreactive T-cell responses associated with not only an increased risk of acute GVHD[4] but also a reduced risk of leukemic relapse due to the GVL.[5] As HLA-DPB1 mismatch is observed in >80% of UD-recipient pairs, the definition of permissive HLA-DPB1 mismatches (ie, HLA-DPB1 combinations eliciting limited T-cell alloreactivity with a reduced risk of GVHD but maintaining the clinical efficacy of GVL) represents a major challenge and opportunity in HLA-matched UD-HCT. The differentiation between permissive and nonpermissive was achieved by functional matching for T-cell epitope (TCE) groups displaying cross-recognition between different HLA-DPB1 alleles.[6] Permissive HLA-DPB1 mismatches were shown to significantly associated with a lower risk of mortality and relapse after HCT, prompting the inclusion of the HLA-DPB1 TCE algorithm into international donor selection guidelines.[7] However, so far, the detailed mechanisms underlying permissive and nonpermissive HLA-DPB1 mismatch have not been clearly delineated. Based on their own preliminary work suggesting a role of the immunopeptidome presented by different HLA-DPB1 allotypes on TCE permissiveness,[8] Meurer's group investigated the diversity of peptide repertoires in a model of specific permissive vs nonpermissive HLA-DP allelic variant combinations. Comparing different HLA-DP allotypes from 3 TCE groups on different cell lines, they detected a significantly higher overlap between the immunopeptidomes of permissive vs nonpermissive allotype combinations, which resulted in lower frequency and diversity of alloreactive TCRβ clonotypes in healthy donors and patients after HCT. Thus, mass spectrometry–based immunopeptidome and TCRβ clonotype sequencing analyses might contribute to the characterization of permissiveness in currently debated HLA-DPB1 mismatch combinations and also for other HLA loci. Furthermore, it might complement prediction algorithms that relate HLA expression levels with the risk of GVHD after UD-HCT.[9]

Strikingly, further analysis on the mechanistical basis of immunopeptidome diversity in HLA-DP permissive and nonpermissive mismatch identified a central role of the peptide editor HLA-DM. HLA-DM regulates the peptide loading from self-antigens or foreign antigens on HLA class II molecules by catalyzing the removal of the residual HLA class II cleaved invariant chain peptide as well as other weak-binding peptides and their replacement by strong-binding HLA ligands. By preventing the presentation of weak-binding peptides, HLA-DM guides the T-cell response to "immunodominant" regions of antigens, which in the case of self-proteins promotes elimination of potentially autoreactive T cells.[10] Meurer et al showed that the absence of HLA-DM led to an increase in the number and abundance of HLA-DP peptides with a significant increase in T-cell alloreactivity to permissive HLA-DP allotype combinations in healthy donors as well as in patients after HCT. These data underscore the role of HLA-DM peptide editing in the context